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Fertility Preservation in Children, Adolescents, and Young Adults With Cancer: Quality of Clinical Practice Guidelines and Variations in Recommendations

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BACKGROUND: Fertility preservation care for children, adolescents, and young adults (CAYAs) with cancer is not uniform among practitioners. To ensure high-quality care, evidence-based clinical practice guidelines (CPGs) are essential. The authors identified existing CPGs for fertility preservation in CAYAs with cancer, evaluated their quality, and explored differences in recommendations. **METHODS:** A systematic search in PubMed (January 2000–October 2014); guideline databases; and Web sites of oncology, pediatric, and fertility organizations was performed. Two reviewers evaluated the quality of the identified CPGs using the Appraisal of Guidelines for Research and Evaluation II Instrument (AGREE II). From high-quality CPGs, the authors evaluated concordant and discordant areas among the recommendations. **RESULTS:** A total of 25 CPGs regarding fertility preservation were identified. The average AGREE II domain scores (scale of 0%–100%) varied from 15% on applicability to 100% on clarity of presentation. The authors considered 8 CPGs (32%) to be of high quality, which was defined as scores $\geq 60\%$ in any 4 domains. Large variations in the recommendations of the high-quality CPGs were observed, with 87.2% and 88.6%, respectively, of discordant guideline areas among the fertility preservation recommendations for female and male patients with cancer. **CONCLUSIONS:** Only approximately one-third of the identified CPGs were found to be of sufficient quality. Of these CPGs, the fertility preservation recommendations varied substantially, which can be a reflection of inadequate evidence for specific recommendations, thereby hindering the ability of providers to deliver high-quality care. CPGs including a transparent decision process for fertility preservation can help health care providers to deliver optimal and uniform care, thus improving the quality of life of CAYAs with cancer and cancer survivors. *Cancer* 2016;122:2216–23. © 2016 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of *American Cancer Society*. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

KEYWORDS: childhood cancer, evidence-based medicine, fertility preservation, guidelines, pediatric oncology.

INTRODUCTION

Over the last several decades, the survival of patients with childhood cancer has increased significantly due to advances in treatment. In Europe and the United States alone, nearly 80% of children, adolescents, and young adults (CAYAs) survive 5 years from a cancer diagnosis, with the vast majority expected to achieve extended long-term survival into adulthood.^{1,2} As the number of childhood cancer survivors increases, the long-term side effects of treatment gain greater importance. Of particular concern is the substantially elevated risk of fertility impairment after treatment of childhood cancer, especially after treatment with alkylating agents (and similar DNA interstrand cross-linking agents) and/or radiation to fields that

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expose the ovaries or testes.³⁻⁶ Fertility impairment has serious consequences for quality of life among newly diagnosed patients, their parents, and adults surviving childhood cancer.^{7,8}

Interventions currently can be offered to individuals diagnosed with cancer to preserve their fertility potential.^{9,10} Survey data have indicated that many patients, especially females, are not or are inadequately counseled regarding the potential adverse effects of treatment on fertility and even fewer are referred for fertility preservation. Uniformity of counseling and standards for referral are lacking when fertility preservation is offered, which leads to variability in the uptake of these procedures.^{11,12} To ensure that CAYAs who are diagnosed with cancer receive high-quality uniform care, evidence-based clinical practice guidelines (CPGs) are essential. CPGs are defined by the Institute of Medicine as “statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.”¹³ CPGs are important to improve the quality of care and to reduce variability in daily practice and costs.^{14,15} In addition, the design of CPGs bridges the gap between research and clinical practice. However, CPGs in oncology are not always the result of methodologically sound and evidence-based research.¹⁶ A comprehensive assessment of the existing CPGs in fertility preservation for CAYAs with cancer including the variations in recommendations is needed as a first step toward developing an international, uniform, and harmonized CPG.¹⁷ This effort is part of the PanCareLIFE, a European Union-funded project that aims to advance the state-of-the-art in CPGs for fertility preservation counseling by developing CPGs for males and females requiring potentially gonadotoxic cancer treatment modalities and to support health care providers as well as survivors and their families in making informed treatment and intervention choices based on personalized risk assessments.¹⁸ The objective of the current study was to identify existing CPGs for fertility preservation in CAYAs diagnosed with cancer, evaluate their quality, and explore differences in recommendations.

MATERIALS AND METHODS

Identification of Existing CPGs

We explored established national and international guideline databases and organizations known to produce evidence-based CPGs. We also searched CPGs published by oncology and pediatric professional organizations as well as fertility organizations (see online Supporting In-

formation Table S1). In addition, we consulted experts in the field of pediatric oncology and gynecology, and experts in our PanCareLIFE Consortium to identify existing CPGs. We also systematically searched in PubMed for CPGs published between January 1, 2000 and October 1, 2014. The search strategy was developed in collaboration with the Cochrane Childhood Cancer Group, and comprised the following terms: “fertility preservation,” “cancer,” “children/young adult,” and “guidelines” (see online Supporting Information SMethods 1 for full search strategy). Articles were independently selected on the basis of title and abstract by 2 reviewers (A.F.G. and R.L.M.) using the following inclusion criteria: evidence-based CPGs (presenting evidence and recommendations) covering fertility preservation and written in English or Dutch. To avoid being restrictive, we included CPGs for children, adolescents, and adults with cancer. We excluded committee/expert opinion documents and review articles with no recommendations. If the abstract was unavailable electronically or if it provided insufficient information, we retrieved the full-text article for more detailed examination. Discrepancies between review authors were resolved by consensus. Finally, all selected records were assessed in full text by the 2 reviewers (A.F.G. and R.L.M.) to ensure eligibility.

Appraisal of Existing CPGs With Appraisal of Guidelines for Research and Evaluation II Instrument

We appraised the methodology of the identified CPGs using the Appraisal of Guidelines for Research and Evaluation II instrument (AGREE II).¹⁹ AGREE II comprises 23 key items organized into 6 domains. Each domain covers a unique dimension of practice guideline quality: scope and purpose (domain 1); stakeholder involvement (domain 2); rigor of development (domain 3); clarity of presentation (domain 4); applicability (domain 5); and editorial independence (domain 6). All documents related to the guideline (ie, handbook or other supplementary information) were taken into account when appraising the guideline quality.

Each guideline was independently assessed by 2 reviewers by assigning scores on a 7-point scale for each key item. The workload was divided between 3 reviewers (A.F.G. appraised 23 CPGs, R.L.M. appraised 13 CPGs, and E.A.H.L. appraised 14 CPGs). Scoring discrepancies of ≥ 3 points were discussed between the appraisers without the desire to reach consensus but to ensure that no information was missing (see online Supporting Information Table S3 for mean key item scores). Following the formula established by AGREE II, standardized

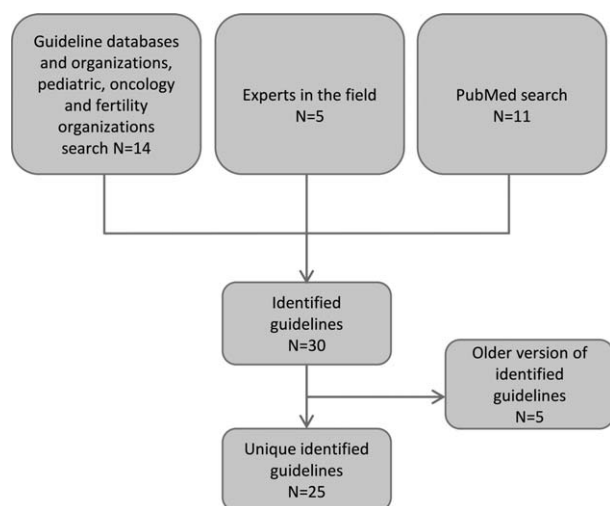


Figure 1. Flowchart shows the results of searches for fertility preservation clinical practice guidelines after a search in guideline databases and organizations; searches in pediatric, oncology, and fertility professional organizations; a consultation with experts in the field of pediatric oncology and gynecology and experts in our PanCareLIFE Consortium; and a systematic literature search in PubMed.

domain scores for each CPG were expressed on a scale of 0% to 100% and calculated by summing scores of individual items and standardizing the total as a percentage of the maximum possible score for that domain.¹⁹ We considered high-quality CPGs to be those that had scores $\geq 60\%$ in any 4 (or more) AGREE II domains. As recommended by AGREE II, we did not measure the overall score that represents a combination of all 6 domains as identifying criteria for high-quality CPG.¹⁹

Comparison of Existing CPGs

To compare the content and evaluate the discordant and concordant areas in the identified high-quality CPGs, we considered the following key questions: “Who should be advised to receive fertility preservation?”, “What fertility preservation method should be used?”, “When should fertility preservation be discussed and initiated?”, “Who should be involved in the counseling and decision making about fertility preservation?”, and “What are the ethical and logistical aspects?”. We subdivided each key issue in specific items or guideline areas outlined in the content of all of the CPGs. Thus, the number of guideline areas varied per key issue. The first and second authors (A.F.G. and R.L.M.) extracted for each guideline area the recommendations from the high-quality CPGs. Any disagreements were discussed and resolved by consensus.

A guideline area was considered as concordant when all CPGs advised the same recommendation for

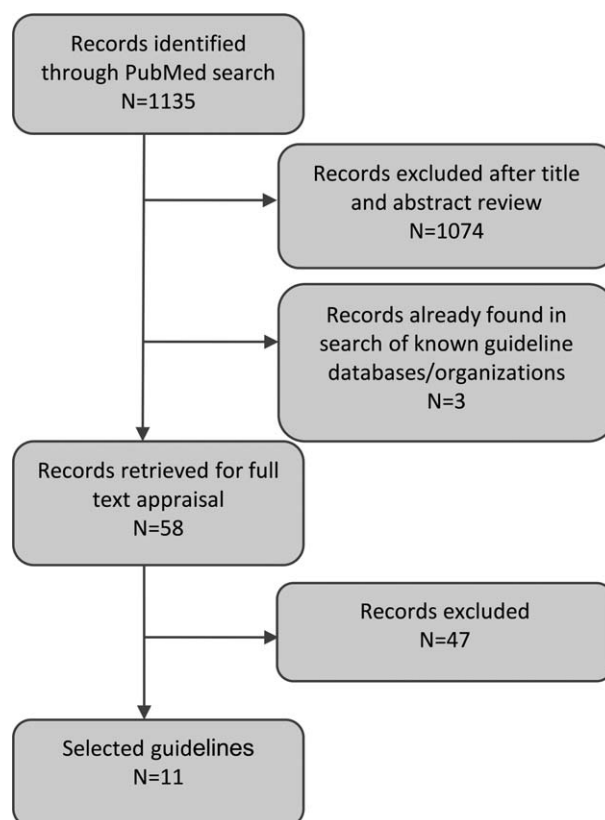


Figure 2. Flowchart shows the number of selected clinical practice guidelines after the PubMed search.

the specific guideline area. If this was not the case, the guideline area was considered discordant. If a CPG did not include a recommendation for a specific guideline area or if only 1 guideline covered a specific guideline area but the rest did not, we also considered that guideline area to be discordant, and we added a comment referring to this situation. If one guideline did not present information at all regarding one key issue, we excluded the guideline when assessing areas of concordance and discordance.

RESULTS

Identified CPGs

In total, we identified 25 unique CPGs (Fig. 1). The search regarding known guideline databases, cancer Web sites, and pediatric and fertility organizations yielded 14 CPGs (see online Supporting Information Table S1). After consulting experts in the field, we identified an additional 5 CPGs. From our systematic search in PubMed, we identified 11 additional CPGs (Fig. 2). We excluded 5 CPGs that were updated versions of CPGs that already had been identified.

TABLE 1. Results of AGREE II in 25 Identified Existing CPGs for Fertility Preservation in Children With Cancer, Including 8 High-Quality CPGs

Guideline	Domain 1: Scope and Purpose	Domain 2: Stakeholder Involvement	Domain 3: Rigor of Development	Domain 4: Clarity of Presentation	Domain 5: Applicability	Domain 6: Editorial Independence
High quality ^a						
NVOG 2007 ²⁰	75%	78%	61%	81%	15%	63%
SIGN 2011 ²¹	92%	89%	79%	97%	69%	54%
Fernbach 2014 ²²	89%	53%	66%	97%	15%	63%
ASCO 2013 ²³	86%	92%	77%	100%	48%	58%
NICE 2013 ²⁴	94%	83%	98%	94%	83%	71%
SIGN 2013 ²⁵	97%	83%	69%	100%	67%	79%
NCCN 2014 ²⁶	69%	61%	68%	94%	15%	67%
COSA 2011 ²⁷	92%	81%	66%	100%	29%	38%
Overall (mean)	87%	78%	73%	95%	43%	62%
Lower quality						
BFS 2003 ²⁸	53%	44%	13%	72%	21%	0%
EGCCCG 2004 ²⁹	53%	22%	23%	47%	10%	0%
Wallace 2005 ³⁰	39%	8%	16%	39%	4%	29%
RCP 2007 ³¹	50%	56%	18%	86%	21%	0%
Backhus 2007 ³²	42%	22%	4%	31%	4%	8%
AAP 2008 ³³	25%	8%	10%	44%	17%	25%
Tangjitgamol 2009 ³⁴	64%	11%	26%	50%	10%	0%
IKNL 2009 ³⁵	61%	53%	33%	58%	6%	38%
Cardoso 2012 ³⁶	58%	31%	35%	75%	8%	25%
Michaeli 2012 ³⁷	47%	17%	8%	50%	0%	0%
ISFP 2012 ³⁸	42%	19%	11%	56%	4%	0%
EAU 2015 ³⁹	42%	47%	55%	89%	29%	92%
ASRM 2013 ⁴⁰	58%	28%	42%	86%	15%	54%
AHS 2013 ⁴¹	86%	28%	53%	89%	23%	71%
BCSH 2014 ⁴²	61%	36%	49%	97%	8%	29%
ISFP 2012 ⁴³	36%	8%	15%	42%	8%	25%
NZ 2014 ⁴⁴	58%	67%	53%	67%	25%	0%

Abbreviations: AAP, American Academy of Pediatrics; AGREE II, Appraisal of Guidelines for Research and Evaluation II Instrument; AHS, Alberta Health Services; ASCO, American Society of Clinical Oncology; ASRM, American Society for Reproductive Medicine; BCSH, British Committee for Standards in Haematology; BFS, British Fertility Society; COSA, Clinical Oncology Society of Australia; CPG, clinical practice guideline; EAU, European Association of Urology; EGCCCG, European Germ Cell Cancer Consensus Group; ISFP, International Society for Fertility Preservation; IKNL, Integraal Kankercentrum Nederland [Netherlands Comprehensive Cancer Organisation]; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Clinical Excellence; NVOG, Nederlandse Vereniging voor Obstetrie en Gynaecologie [Dutch Association for Obstetrics and Gynecology]; NZ, National Child Cancer Network New Zealand; RCP, Royal College of Physicians; SIGN, Scottish Intercollegiate Guidelines Network.

^a Guidelines that met the criteria to be considered high quality (ie, with $\geq 60\%$ in any 4 domains).

AGREE II Appraisal

We appraised the quality of the 25 identified CPGs using AGREE II (Table 1).²⁰⁻⁴⁴ All CPGs identified were written in English with the exception of 2 CPGs that were written in Dutch.^{20,35}

CPGs varied with regard to the extent of information provided concerning fertility preservation. Some CPGs provided comprehensive information regarding fertility preservation for patients with cancer (such as the American Society of Clinical Oncology (ASCO)²³) whereas others did not (eg, the Scottish Intercollegiate Guidelines Network [SIGN]²¹). The majority of CPGs addressed all cancer types, with the exception of 8 CPGs that focused on specific cancer types including breast cancer (1 CPG), germ cell tumors (3 CPGs), Hodgkin lymphoma (2 CPGs), hematological tumors (1 CPG), and endometrial tumors (1 CPG). The majority of CPGs (14

CPGs) considered fertility preservation for both sexes, whereas others focused exclusively on either female (8 CPGs) or male (3 CPGs) patients with cancer (see online Supporting Information Table S2). Eight of the 25 CPGs met the criteria to be considered a high-quality CPG (ASCO,²³ Fernbach et al,²² National Institute for Health and Clinical Excellence [NICE],²⁴ National Comprehensive Cancer Network (NCCN),²⁶ SIGN [2011],²¹ SIGN [2013],²⁵ Clinical Oncology Society of Australia (COSA),²⁷ and Nederlandse Vereniging voor Obstetrie en Gynaecologie [Dutch Association for Obstetrics and Gynecology] (NVOG)²⁰) (Table 1).²²⁻⁴⁰ The mean item scores in each CPG are shown in Supporting Information Table S3. Overall, the highest mean domain score was for clarity of presentation (95%) and the lowest was noted for applicability (43%) (see online Supporting Information SMethods 2).

TABLE 2. Concordant and Discordant Guideline Areas in High-Quality Female Fertility Preservation CPGs

	Concordant ^a	% per Row	Discordant ^b	% per Row	Total
Who should be advised to receive fertility preservation?	3	27.3	8	72.7	11
What fertility preservation method should be used?	1	14.3	6	85.7	7
When should fertility preservation be discussed and initiated?	1	14.3	6	86	7
Who should be involved in the counseling and decision making regarding fertility preservation?	1	7.7	12	92.3	13
What are the ethical and logistical aspects?	0	0.0	9	100	9
Total	6	12.8	41	87.2	47

Abbreviation: CPG, clinical practice guideline.

^a Concordant guideline areas were those that presented the same recommendation in all CPGs.

^b Discordant guideline areas were those that did not present the same recommendation in all CPGs, those guideline areas that did not have a recommendation, or if only 1 CPG covered a guideline area.

TABLE 3. Concordant and Discordant Guideline Areas in High-Quality Male Fertility Preservation CPGs

	Concordant ^a	% per Row	Discordant ^b	% per Row	Total
Who should be advised to receive fertility preservation?	2	20.0	8	80.0	10
What fertility preservation method should be used?	1	12.5	7	87.5	8
When should fertility preservation be discussed and initiated?	1	12.5	7	87.5	8
Who should be involved in the counseling and decision making about fertility preservation?	0	0.0	13	100.0	13
What are the ethical and logistical aspects?	1	20.0	4	80.0	5
Total	5	11.4	39	88.6	44

Abbreviation: CPG, clinical practice guideline.

^a Concordant guideline areas were those that presented the same recommendation in all CPGs.

^b Discordant guideline areas were those that did not present the same recommendation in all CPGs, those guideline areas that did not have a recommendation, or if only 1 CPG covered a guideline area.

Concordant and Discordant Fertility Preservation Guideline Areas

Tables 2 and 3 as well as online Supporting Information Tables S4 and S5 show the concordant and discordant guideline areas among the high-quality CPGs. In both males and females, recommendations for several specific guideline areas were not mentioned. Overall, for female fertility preservation, there was concordance among 6 of 47 guideline areas (12.8%) and discordance among 41 of 47 guideline areas (87.2%). Of the 6 concordant guideline areas, the highest concordance rate was for the key issue “Who should be advised to receive fertility preservation?” (50%), followed by the key issue “What fertility preservation method should be used?” (16.7%), “When should fertility preservation be discussed and initiated?” and “Who should be involved in the discussion of and decision for fertility preservation?” (16.7%). The highest discordance rate was found for the key issue “Who should be involved in the counseling and decision making about fertility preservation?” (29.3%). We observed no concordant areas for the key issue “What are the ethical and logistical aspects?”.

With regard to male fertility preservation CPGs, we observed overall concordances in 5 of 44 guideline areas (11.4%) and discordance in 39 of 44 guideline areas (88.6%). The highest concordance rate was found for the

key issue “Who should be advised to receive fertility preservation?” (40%), followed by the key issues “What fertility preservation method should be used?” (20%), “When should fertility preservation be discussed and initiated?” (20%), and “What are the ethical and logistical aspects?” (20%). The key issue “Who should be involved in the counseling and decision making about fertility preservation?” presented no concordant areas.

DISCUSSION

In the current study, we observed considerable variability among the recommendations of the selected high-quality CPGs addressing fertility preservation. The lack of quality and uniformity in the recommendations is likely to lead to conflicting recommendations and reflects that the quality of clinical practice may not be optimal for all patients with cancer.⁴⁵ This supports the need for well-developed and transparently harmonized CPGs for CAYAs diagnosed with cancer who are at risk of fertility impairment.

The guideline recommendations exhibited discordance in 87.2% and 88.6%, respectively, of issues addressed for female and male patients with cancer. This discordance relates to conflicting recommendations between guidelines and also to some of the guidelines

omitting recommendations for specific guideline areas. The lack of available evidence or the low level of existing evidence in the field of fertility preservation for CAYAs with cancer is very likely to contribute to the variation observed. Future research studies in this evolving field of clinical cancer practice will help to improve the available evidence, thereby contributing to more comprehensive fertility preservation CPGs. Although nearly all CPG recommendations included the need to involve the multidisciplinary team in counseling and decision making regarding fertility preservation, not all of them explicitly mentioned the need for the involvement of patients, parents, and advocacy groups in the discussions. A systematic review revealed data indicating that adolescents are very keen to be part of decisions related to their cancer treatment and many have worries about their fertility, but additional research is needed to explore the content of the counseling and the role of adolescents and parents with regard to fertility.⁴⁶

We observed no concordance related to the key issue “What are the ethical and logistical aspects?” in recommendations for female patients with cancer and only 1 concordant guideline area for recommendations for male patients with cancer. The unique ethical issues surrounding fertility preservation discussions with minors and discussions of experimental treatments involve a considerable amount of uncertainty and can play a role in these variations.⁴⁷ Another likely explanation is national differences in the legal aspects of informed consent; storage of oocytes, embryos, ovarian tissue, and sperm; and the costs involved with the procedures. As an example, we observed that the NVOG recommended that oocytes, embryos, and ovarian tissue be stored for a period of up to 40 years whereas NICE recommended a maximum of 55 years, with an initial period of 10 years. We found a high degree of concordance for the guideline areas covering fertility preservation methods and populations at risk of fertility impairment. Although all CPGs that recommended ovarian tissue cryopreservation included a statement concerning its experimental nature, the NICE guideline did not explicitly recommend this procedure because of the lack of evidence to support future successful fertility based on their literature searches. In addition, all the CPGs that included ovarian tissue cryopreservation in their recommendations mentioned the risk of reintroducing malignant cells with grafting. The CPG from the COSA explicitly included the recommendation to test the ovarian tissue for the presence of cancer cells or markers.

Only approximately one-third of the identified CPGs concerned with fertility preservation for CAYAs with cancer met our criteria for high quality. Our critical assessment

of the CPG methodology revealed very low AGREE II domain scores on guideline implementation. Although tools to facilitate application such as summary documents and links to algorithms were often found in the high-quality CPGs, pilot testing of the guideline recommendations or criteria to assess the impact of the implementation and usability of the application tools were lacking. Similar findings have been shown when assessing the quality of oncology⁴⁸ and pediatric⁴⁹ CPGs in general. This highlights the importance of establishing strategies during the guideline development process that can improve adherence to the recommendations. Some authors have warned of the risks of large investments to develop and disseminate CPGs without successful implementation, and emphasized the need for an approach that integrates not only physicians as stakeholders but also patients.⁵⁰

Although the CPG by Fernbach et al²² was considered high quality, it scored very low on the domains of stakeholder involvement and applicability. This is likely to be related to the fact that the intent of their CPG was to produce a summary of recommendations supported by evidence using a rigorous development method, but not to develop an official CPG.

We found that the Australian guideline²⁷ scored the lowest for the domain of editorial independence. Competing risks of authors or funding bodies may have had an influence on the recommendations for fertility preservation we identified. However, because AGREE II only assesses the reported quality of the guideline development, there is a possibility that the criteria were met but not specifically reported.

A strength of the current study was the use of an objective instrument in the form of AGREE II to assess the quality of the CPGs. In addition, we reduced the chance of misinterpretation or missing information with regard to the AGREE II items among the appraisers by discussing in detail the items that differed by ≥ 3 points. One study that also used AGREE II to evaluate guidelines regarding fertility preservation for reproductive-age patients with breast cancer revealed a wide variability in the recommendations.⁵¹ The findings of the current study underscore that the lack of uniformity in recommendations for fertility preservation is not limited to one patient group or tumor type, but exists in CAYAs with all tumor types.

A limitation of the current study was that we only selected CPGs written in English or Dutch, and this implies the risk of potentially missing well-developed non-English or non-Dutch CPGs (selection bias). However, we expect this risk to be small because we asked international experts in the fields of pediatric oncology and gynecology and

within the PanCareLIFE Consortium for additional evidence-based CPGs. Another limitation could be that AGREE II does not differentiate between the relative importance of the domains. However, in our opinion, the AGREE II domains are not equally important. AGREE II does not provide specific advice regarding how to present an overall assessment. Thus, we chose not to provide an overall judgment, which in our opinion is too subjective to report.

The current study was the starting point for the development of a harmonized guideline for fertility preservation within the European PanCareLIFE project. PanCareLIFE is taking steps to generate transparent and cohesive CPGs for fertility preservation for children facing gonadotoxic therapies with the objective of guiding clinical practice internationally by including experts from within and outside Europe. In addition, political, religious, and legal issues surrounding fertility preservation are taken into account in this guideline development project because we involved a multidisciplinary group of experts (including ethicists) in the working groups.

An essential part of the work of the PanCareLIFE Consortium is to establish networks to ensure international expertise and efforts; to avoid duplication of work; to use evidence-based, robust methods; and to harmonize recommendations.¹⁸ Previous international efforts to develop recommendations for the surveillance (not care) of survivors of childhood cancer indicated that such a worldwide endeavor is feasible.¹⁷ The International Guideline Harmonization Group has already published several worldwide, harmonized, evidence-driven surveillance recommendations based on this methodology to decrease discordances between national groups.^{52,53}

The results of the current study indicate that recommendations for fertility preservation vary across fertility preservation CPGs that currently are in place for CAYAs with cancer. It is conceivable that the lack of uniformity in recommendations reflects the inadequate evidence for specific recommendations, thereby hindering the ability of providers to deliver high-quality care. CPGs that include transparent and harmonized advice for fertility preservation counseling can help health care providers to deliver optimal and uniform care that may translate into a quality-of-life benefit for CAYA patients with cancer and cancer survivors.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

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